Remarks

Upon entry of the foregoing amendment, claims 157-294 will be pending in the application. Claims 157, 173, 176, 180, 196, 199, 207, 210, 229, 230, 231, 232, 236, 239, 247, 250, 257, 260, 264, 273, 276, 280 and 288 have been amended taking the Examiner's comments into consideration. This amendment introduces no new matter and entry thereof is respectfully requested. Applicants reserve the right to pursue the subject matter of the unamended claims in continuing applications.

Support for the amended claims can be found throughout the specification. Support can be found, *inter alia*, at pages 11-15; at page 16, lines 4-18; and at pages 97-100.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Specification

The Examiner objected to the specification as allegedly failing to provide proper antecedent basis for the claimed subject matter. (Paper No. 34, at page 2.) According to the Examiner, "[t]here is no antecedent basis in the specification as originally filed for claims 159, 162, 165, 168, 182, 185, 188, 191, 229, and 231" and "new claims broadly reciting 'at least 90% identity' in the absence of a recited 'essential property' are not supported in the original disclosure, and accordingly are rejected under 35 USC 112, first paragraph for the introduction of new matter." *Id.* at pages 2-3. Applicants respectfully traverse this rejection.

Without admitting to the Examiner's allegation, and solely in the interest of

facilitating prosecution, Applicants have amended the claims to recite that the encoded polypeptide regulates Prostate-Specific Antigen (PSA) gene expression. Thus, the 90% and 95% identity claims as currently claimed are supported in the original disclosure, *inter alia*, at pages 11-15. Accordingly, this amendment should overcome the objection. Applicants reserve the right to pursue the subject matter of the unamended claims in continuing applications.

Rejections under 35 U.S.C. § 112

Written description

Claims 157-158, 161, 164, 167, 170-181, 184, 187, 190, 193-202, 207-208, 210-211, 236-237, 239-240, 247-248, 250-251, 257-258, 260-261 and 264-294 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (Paper No. 34, at page 3.)

Regarding claims 157-158, 161, 164, 167, 170-181, 184, 187, 190 and 193-202, the Examiner alleged that "[t]he claims do *not* recite that the polynucleotides or the polypeptides they encode retain 'essential properties' of PDEF polynucleotides or polypeptides. Applicant has not indicated or explained where the specification supports these new claims." *Id.* (emphasis in original). Applicants respectfully traverse this rejection.

Applicants submit that the specification *does* support variant PDEF polypeptides that do not retain biological activity. For example, the specification teaches that variant polypeptides, including deletions, insertions, inversions, repeats and substitutions, will likely

retain the ability to induce and/or to bind antibodies which recognize the protein of SEQ ID NO:2. *See* the specification at page 16, lines 4-18.

However, solely in an effort to facilitate prosecution, Applicants have amended the claims to recite that the nucleic acid encodes a polypeptide that regulates Prostate-Specific Antigen (PSA) gene expression. Support for this amendment can be found, *inter alia*, at pages 11-15 and 97-100. Accordingly, withdrawal of this rejection is respectfully requested. Applicants point out that the amendment to the claims renders the rejection of claims 173 and 174 (at pages 5-6 of Paper No. 34) moot. Applicants reserve the right to pursue the subject matter of the unamended claims in continuing applications.

Regarding claims 176, 196, 199, 207, 210, 236, 239, 247, 250, 260, 273 and 276, the Examiner alleged that "[w]hile the specification fully supports the linkage between heterologous sequences in general to the first nucleic acid, the same cannot be said for an 'operable linkage'." (Paper No. 34, at page 5.) Applicants respectfully traverse this rejection.

However, solely in an effort to advance prosecution, Applicants have deleted the term "operable" from the claims. Thus, the claims as amended herein do not recite that the first nucleic acid is "operably associated" with a heterologous sequence. Accordingly, withdrawal of this rejection is respectfully requested. Applicants reserve the right to pursue the subject matter of the unamended claims in continuing applications.

The Examiner further argued that "[t]he 'an enhancer, a Kozak sequence, an operator' elements recited in the claims were not included in the original specification with the other specific sequences recited in the claims, and are unsupported." (Paper No. 34, at page 5.)

Applicants respectfully disagree. The elements recited in the claims, such as, an enhancer, a Kozak sequence and an operator are part of expression vectors disclosed as

being part of the invention. For example, the specification teaches, *inter alia*, at page 54, lines 15-23, and at page 59, lines 8-20, that the present invention includes expression vectors comprising a phage operator, signals for termination of transcription and polyadenylation, enhancers, Kozak sequences and promoter elements operatively linked to a PDEF polynucleotide. *See also* page 52, lines 21-30; page 56, lines 20-31; page 57, lines 1-15; page 60, lines 7-14; page 93, lines 26-28; page 94, lines 17–18; and page 99, lines 17-19 and 24-26. Thus, the elements recited in the claims were included in the original specification with the other sequences recited in the claims and are fully supported. Accordingly, withdrawal of this rejection is respectfully requested.

Regarding claims 264-279, the Examiner stated that

> [a]s written, the claims appear to be directed to disclosed embodiments where the polynucleotide encodes a fusion protein comprising the heterologous polypeptide and an epitope sequence from SEQ ID NO:2. However, the claim does not recite such a relationship between the "nucleic acid" and the "nucleotide sequence", the polynucleotide need not encode any fusion protein; and consequently is not supported by the specification. This part of the rejection would be overcome by inserting --in frame-- after "fused" in line 1 of claim 264 . . . .

Paper No. 34, at page 6. Although Applicants do not agree with the Examiner, they have adopted the Examiner's suggestion. Accordingly, this rejection has been rendered moot. Applicants point out that the amendment does not narrow the claim in any way since Applicants intended to claim a fusion protein. In addition, Applicants reserve the right to pursue the subject matter of the unamended claims in continuing applications.

Regarding claims 288-294 directed to epitopes of PDEF, the Examiner stated that "[t]here is no support in the original specification for such 'operative association'. The specification only describes recombinant expression of the epitopes when they are fused to

some other polypeptide sequence" and "[a]mending claim 288 to include the limitations of claim 264, lines 1-4, (either as a claim dependent from claim 264 or as an independent claim) would overcome this part of the rejection." (Paper No. 34, at page 7.) Applicants respectfully traverse this rejection.

However, in an effort to advance prosecution, Applicants have amended claim 288 to include the limitations of claim 264, lines 1-4, as the Examiner suggested. Accordingly, this rejection has been rendered moot. Applicants reserve the right to pursue the subject matter of the unamended claims in continuing applications.

Enablement

The Examiner rejected claims 180-182, 184-185, 187-188, 190-191, 193-202, 229, 231 and 233-242 under 35 U.S.C. § 112, first paragraph, because allegedly, "the specification, while enabling for a 'nucleic acid' that encodes SEQ ID NO:2 or a fragment of SEQ ID NO:2 (as recited in the claims), does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO:2 or a recited fragment of SEQ ID NO:2." (Paper No. 34, at page 7.) According to the Examiner,

> [a]ll of the utilities for polynucleotides taught in the specification require that either the polynucleotide will hybridize with a PDEF nucleic acid or that it encode a polypeptide, either with PDEF function or that can be used to make antibodies that will be specific for a PDEF protein. The specification does not teach any use for a polynucleotide that cannot be used for these purposes.

Paper No. 34, at page 8. Applicants respectfully traverse this rejection.

Contrary to the Examiner's position, the specification teaches numerous additional utilities for the claimed polynucleotides. For example, the specification, at pages 29-33 and

46, teaches that polynucleotides can be used as primers or probes for *in situ* hybridization; in Northern blot analysis; to control gene expression through triple helix formation or antisense DNA or RNA; for gene therapy; for identifying individuals through restriction fragment length polymorphism (RFLP) analysis; to identify DNA sequences which are targets for PDEF; and to identify novel target genes by cDNA array transcriptional profiling. Thus, numerous additional utilities are disclosed. Applicants point out that to be fully enabled, the claimed polynucleotides are not required to have biological activity.

The Examiner further contended that "[t]he specification does not teach that one should make such variants for the purpose of making antibodies against human PDEF (SEQ ID NO:2); nor is there any evidence of record that one skilled in the art would even consider such a method in the absence of such a disclosure." (Paper No. 34, at page 10.) Applicants respectfully disagree.

As discussed *supra*, the specification *does* teach that variant polypeptides, including deletions, insertions, inversions, repeats and substitutions, will likely retain the ability to *induce* and/or to *bind* antibodies which recognize the protein of SEQ ID NO:2. *See* the specification at page 16, lines 4-18. Therefore, the specification does teach that variants can be used for the purpose of making antibodies against the polypeptide of SEQ ID NO:2.

Furthermore, the Examiner has not provided any evidence that one skilled in the art would not consider using variants to make antibodies against the native protein. In fact, as Applicants indicated in the reply filed on July 24, 2001, it is well established that such variants would be useful to examine the protein of SEQ ID NO:2. For example, it is well established in the art of molecular biology that such variants can be routinely made and used in epitope-mapping studies. *See, e.g.*, Ikeda *et al.*, "Epitope mapping of anti-recA protein

IgGs by region specified polymerase chain reaction mutagenesis," *J. Biol. Chem. 267*:6291-6296 (1992)(copy submitted with the reply filed on July 24, 2001). The experimentation required to make and use such polynucleotides requires little if any ingenuity and, similar to the situation in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988), is merely routine experimentation for one skilled in the art of molecular biology.

The Examiner further alleged that "[i]t is unclear how one skilled in the art could predict which of all the possible variant amino acid sequences could be used to make a suitable antibody to the PDEF protein, and the specification provides no guidance on the matter." (Paper No. 34, at page 10.) Applicants respectfully disagree.

First of all, "[t]here is no magical relation between the number of representative examples and the breadth of the claims" with respect to enablement. *In re Borkowski*, 422 F.2d 904, 910, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). The issue is not whether the specification discloses all possible PDEF polypeptide fragments that can be used to make antibodies to the PDEF protein, but rather whether additional PDEF polypeptide fragments would be expected to be useful to make antibodies to the PDEF protein, and whether such polypeptide fragments can be determined, without undue experimentation, by following procedures either described in the specification or otherwise known in the art. It is thus not necessary to disclose all peptide fragments of PDEF that can be used to make antibodies to the PDEF protein, or to limit the claims to the specific polypeptide sequences disclosed in the specification to make antibodies. *See In re Angstadt*, 537 F.2d 498, 502-503, 190, U.S.P.Q. 214, 218 (C.C.P.A. 1976): "To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a

prohibitive number of actual experiments . . . ." *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*.

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 U.S.P.Q. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." Since the disclosed or otherwise known methods of making and screening the claimed polypeptides may be used to determine, without undue experimentation, whether a given polypeptide encompassed by the claims can be used to make antibodies, the enablement requirement is fully satisfied. *In re Wands*, 858 F.2d at 738, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

Furthermore, the specification provides, *inter alia*, at page 25, predicted antigenic regions that comprise epitope-bearing portions of the PDEF protein. One of ordinary skill in the art looking at the PDEF sequence would know which amino acid residues encoded by

the polynucleotide of the claims could be substituted and still constitute a polypeptide which is capable of raising antibodies to the PDEF protein, and could routinely make and use the polypeptides to raise antibodies. Applicants need not disclose every species encompassed by a claim to satisfy the requirements of 35 U.S.C. § 112. *In re Angstadt*, 190 USPQ 214, 218 (C.C.P.A. 1976).

The Examiner also alleged that "the specification does not identify any other naturally occurring PDEF polypeptides, such as homologues from other mammals or allelic variants from other humans or any other mammals, whose sequence is within the window encompassed by the claims other than that set forth in SEQ ID NO:2." (Paper No. 34, at page 9.) Applicants respectfully disagree.

The specification discloses at, *inter alia*, page 8, a *Drosophila* homologue called ETS-4 and provides an alignment of PDEF and ETS-4 in Figure 2. Thus, one skilled in the art looking at Figure 2 and comparing the sequences of PDEF and *Drosophila* ETS-4 will understand that areas of identity (shaded amino acids) or conserved areas (boxed amino acids) are likely to be critical for function and therefore should not be altered, and that areas of no or lesser homology are likely to be tolerant of alterations.

Furthermore, the specification describes phenotypically silent amino acid substitutions (*see* page 16, lines 15-31), and the genetic code is known. Based on the various teachings in the specification, one skilled in the art of molecular biology can thus easily predict the amino sequence of derivatives that can induce and/or bind antibodies that bind the protein of SEQ ID NO:2 or that encode a biologically active PDEF protein. The specification provides several assays, *inter alia*, at pages 97-100, which can be used to assess function. Such experimentation requires little if any ingenuity and is merely routine

experimentation for one skilled in the art of molecular biology. Thus, no "excessive trial and error experimentation would be required."

The Examiner also compared the current situation to that in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), stating that

> the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where [the] specification discloses only a single amino acid sequence, SEQ ID NO:2, for a polypeptide having the necessary properties for the disclosed uses, i.e. encoding an active PDEF protein or a polypeptide that could be used to make antibodies against a PDEF polypeptide, and provides no guidance on predicting polypeptide variants of SEQ ID NO:2 which would be suitable.

Paper No. 34, at page 12. Applicants respectfully disagree.

The situation here is substantially different from that in Amgen. First of all, the claim at issue in Amgen (claim 7), is a generic claim covering all possible DNA sequences that would encode *any* polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of reticulocytes and red blood cells. *See id.* at 1019. No percent identity is recited in Amgen's claim. In contrast, Applicants' claims are to nucleic acids encoding an amino acid sequence at least 90% identical to SEQ ID NO:2. Furthermore, Applicants' claims as amended herein recite that the amino acid sequence regulates Prostate-Specific Antigen (PSA) gene expression. Thus, unlike the situation in Amgen, Applicants are not claiming all possible DNA sequences, but only a

specific subset, *e.g.*, those that encode an amino acid sequence at least 90% identical to SEQ ID NO:2 and capable of regulating Prostate-Specific Antigen (PSA) gene expression.

Secondly, the Fed. Cir. in Amgen specifically points out that

> it is not necessary that a patent application test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all the Wands factor to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (citations omitted). Thus, basically each case is decided on its facts.

The facts in Amgen are substantially different from the facts in the current application. Amgen's claims are "all-encompassing," claiming *any* DNA sequence "sufficiently duplicative" to that of EPO, having EPO activity. In contrast, Applicants claim, *inter alia*, DNA sequences that encode a polypeptide that is 90% identical to the amino acid sequence of SEQ ID NO:2. Furthermore, Applicants' specification, as discussed *supra*, provides ample guidance to allow one skilled in the art to predict polypeptide variants of SEQ ID NO:2 that are 90% identical, which would regulate Prostate-Specific Antigen (PSA) gene expression. Thus, the teachings in the specification *are* sufficient to enable one skilled in the art to make and use the claimed invention without undue experimentation. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Allowable Subject Matter

The indication that claims 203-206, 209, 212-228, 243-246, 249, 252-256 and 259 are allowed is noted and appreciated by Applicants. (Paper No. 34, at page 13.) The Examiner further indicated that claims 159-160, 162-163, 165-166, 168-169, 183, 186, 189, 192, 230 and 232 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. *Id.*

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

The following claims 157, 173, 176, 180, 196, 199, 207, 210, 229, 230, 231, 232, 236, 239, 247, 250, 257, 260, 264, 273, 276, 280 and 288 were substituted for pending claims 157, 173, 176, 180, 196, 199, 207, 210, 229, 230, 231, 232, 236, 239, 247, 250, 257, 260, 264, 273, 276, 280 and 288:

157. (Once amended) An isolated polynucleotide comprising a first nucleic acid at least 90% identical to a reference nucleic acid selected from the group consisting of:

(a) a nucleic acid consisting of nucleotides 839 to 1048 of SEQ ID NO:1;

(b) a nucleic acid consisting of nucleotides 419 to 1420 of SEQ ID NO:1;

(c) a nucleic acid consisting of nucleotides 416 to 1420 of SEQ ID NO:1;

and

(d) a nucleic acid consisting of the nucleotides encoding the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 203072;

<u>wherein said first nucleic acid encodes a polypeptide that regulates Prostate-Specific Antigen (PSA) gene expression</u>.

173. (Once amended) The vector of claim 172, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

176. (Once amended) The host cell of claim 175, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

180. (Once amended) An isolated polynucleotide comprising a nucleic acid encoding a first amino acid sequence at least 90% identical to a reference amino acid sequence selected from the group consisting of:

(a) amino acids 142 to 211 of SEQ ID NO:2;

(b) amino acids 2 to 335 of SEQ ID NO:2;

(c) amino acids 1 to 335 of SEQ ID NO:2; and

(d) the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 203072; wherein said first amino acid sequence regulates Prostate-Specific Antigen (PSA) gene expression.

196. (Once amended) The vector of claim 195, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

199. (Once amended) The host cell of claim 198, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

207. (Once amended) The vector of claim 206, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

210. (Once amended) The host cell of claim 209, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

229. (Once amended) An isolated polynucleotide comprising a first nucleic acid at least 95% identical to a nucleic acid encoding at least 100 contiguous amino acids of SEQ ID NO:2; wherein said first nucleic acid encodes a polypeptide that regulates Prostate-Specific Antigen (PSA) gene expression.

230. (Once amended) [The] An isolated polynucleotide [of claim 229,] comprising a nucleic acid encoding at least 100 contiguous amino acids of SEQ ID NO:2.

231. (Once amended) [An] The isolated polynucleotide of claim 229, comprising a nucleic acid [at least 95% identical to a nucleic acid] encoding at least 150 contiguous amino acids of SEQ ID NO:2.

232. (Once amended) The isolated polynucleotide of claim [231] 230, comprising a nucleic acid encoding at least 150 contiguous amino acids of SEQ ID NO:2.

236. (Once amended) The vector of claim 235, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

239. (Once amended) The host cell of claim 238, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

247. (Once amended) The vector of claim 246, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

250. (Once amended) The host cell of claim 249, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

257. (Once amended) The vector of claim 256, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

260. (Once amended) The host cell of claim 259, wherein said first nucleic acid is [operably] associated with a heterologous sequence.

264. (Once amended) A polynucleotide comprising a nucleic acid fused <u>in frame</u> to a nucleotide sequence heterologous to SEQ ID NO:1, wherein said heterologous nucleotide sequence encodes a heterologous polypeptide, and wherein said nucleic acid is selected from the group consisting of:

(a) a nucleic acid encoding amino acids 279 to 287 of SEQ ID NO:2;

(b) a nucleic acid encoding amino acids 292 to 300 of SEQ ID NO:2;

(c) a nucleic acid encoding amino acids 317 to 325 of SEQ ID NO:2;

(d) a nucleic acid encoding amino acids 239 to 247 of SEQ ID NO:2;

(e) a nucleic acid encoding amino acids 272 to 280 of SEQ ID NO:2; and

(f) a nucleic acid encoding amino acids 248 to 331 of SEQ ID NO:2.

273. (Once amended) The vector of claim 272, wherein said nucleic acid is [operably] associated with a heterologous sequence.

276. (Once amended) The host cell of claim 275, wherein said nucleic acid is [operably] associated with a heterologous sequence.

280. (Once amended) An isolated polynucleotide comprising a nucleic acid encoding at least 60 contiguous amino acids of SEQ ID NO:2;

wherein said nucleic acid is [operably] associated with a heterologous sequence selected from the group consisting of a promoter, a site for transcription initiation, a site for transcription termination, an enhancer, a Kozak sequence, an operator and a ribosome binding site.

288. (Once amended) A polynucleotide comprising a nucleic acid <u>fused to a nucleotide sequence heterologous to SEQ ID NO:1, wherein said heterologous nucleotide sequence encodes a heterologous polypeptide, and</u> [,]wherein said nucleic acid is selected from the group consisting of:

(a) a nucleic acid encoding amino acids 279 to 287 of SEQ ID NO:2;

(b) a nucleic acid encoding amino acids 292 to 300 of SEQ ID NO:2;

(c) a nucleic acid encoding amino acids 317 to 325 of SEQ ID NO:2;

(d) a nucleic acid encoding amino acids 239 to 247 of SEQ ID NO:2;

(e) a nucleic acid encoding amino acids 272 to 280 of SEQ ID NO:2; and

(f) a nucleic acid encoding amino acids 248 to 331 of SEQ ID NO:2;

wherein said nucleic acid is operatively associated with a promoter to express said amino acids.